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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
PETER VAN VLASSELAER and J. WOODRUFF EMLEN

Appeal 2008-1876
Application 09/747,383
Technology Center 1600

Decided: October 28, 2008

Before ERIC GRIMES, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 16-23 and 25-28. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to an aerosol solution of γ-IFN. Claim 22 is representative of the claims on appeal, and reads as follows:

22. A liquid-droplet aerosol composition formed from an aqueous γ-IFN solution having a known, γ-IFN biological activity, and comprising a dispersing agent and a stabilizing agent in an amount effective to stabilize the γ-IFN upon aerosolization, wherein the stabilizing agent consists of a sugar, an alcohol, or an amino acid, wherein the liquid-droplet aerosol composition has

(a) defined-size droplet particles in a selected size range selected from the group consisting of (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, and (v) greater than 10 microns;

(b) a γ-IFN biological activity substantially the same as that of the aqueous γ-IFN solution; and

(c) a γ-IFN molecular size distribution substantially the same as that of the aqueous γ-IFN solution.

The Examiner relies on the following references:

Hora	US 5,078,997	Jan. 7, 1992
Huland	US 5,780,012	Jul. 14, 1998
Nayar	US 5,874,408	Feb. 23, 1999
Ruskewicz	US 5,971,951	Oct. 26, 1999

H. Ari Jaffe et al., *Organ Specific Cytokine Therapy,* 88 J. OF CLINICAL INVESTIGATION, 297-302 (1991).

Peter F. Weller et al., *Accessory Cell Function of Human Eosinophils,* 150 J. OF IMMUNOLOGY, 2554-2562 (1993).

Robert J. Debs et al., *Lung-Specific Delivery Of Cytokines Induces Sustained Pulmonary And Systemic Immunomodulation In Rats,* 140 J. OF IMMUNOLOGY, 3482-3488 (1988).

We affirm.

ISSUE (Indefiniteness)

The Examiner contends that claims 16-23 and 25-28 are indefinite under 35 U.S.C. § 112, second paragraph (Ans. 9). Specifically, the Examiner objects to the language "biological activity substantially the same," and "molecular size distribution substantially the same," as it is unclear if they are the same or within a range (Ans. 9).

Appellants contend that a "claim limitation employing the term 'substantially' has been previously determined [by the Court of Appeals for the Federal Circuit] not to be indefinite under 35 U.S.C. 112, second paragraph," as "the claim limitation was to [be] read in light of the general guidelines in the specification and the meaning ascribed to the term 'substantially' by one skilled in the art." (App. Br. 9.)

Thus, the issue on Appeal is: Does the use of the term "substantially" render claim 22, and therefore also dependent claims 16-21, 23 and 25-28 indefinite?

PRINCIPLES OF LAW

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Claims are in compliance with 35 U.S.C. § 112, second paragraph, if "the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986).

ANALYSIS

We agree with Appellants' analysis, and conclude that the ordinary artisan would understand the metes and bounds of the term "substantially" in view of the teachings of the Specification. For example, the Specification teaches the invention relates to "a method of forming an aqueous aerosol of γ-IFN," wherein the objective of "little or no loss of biological activity or change in molecular state of the γ-IFN" is "reliably obtained." (Spec. 6-7). Thus, in view of that statement in the Specification, the ordinary artisan would understand that "biological activity substantially the same," and "molecular size distribution substantially the same," would mean that there is "little or no loss of biological activity or change in molecular state of the γ-IFN."

Moreover, the Examiner's objection to the term "substantially" seems to be based on the perception that the use of that term *per se* renders the claim indefinite, as the Examiner did not explain why the ordinary artisan would not understand the metes and bounds of the claim in view of the teachings of the Specification.

CONCLUSION OF LAW

We conclude that the use of the term "substantially" does not render claim 22 indefinite, and the rejection is reversed.

ISSUE (Obviousness)

The Examiner contends that claims 16-23 and 25-28 are rendered obvious by the combination of Huland, Debs, and Ruskewicz, as further

evidenced by Nayar or Hora, or by the combination of Huland, Jaffe, Debs, and Ruskewicz, as further evidenced by Nayar or Hora.

Appellants contend that none of the cited references teach a γ-IFN composition having the claimed particle size, also further contending that the cited references do not teach substantially the same γ-IFN activity compared with the liquid prior to aerosolization nor a composition of γ-IFN with substantially the same molecular size distribution after aerosolization.

Thus, the issue on Appeal is: Has the Examiner established a prima facie case of obviousness as to a γ-IFN aerosol composition having the claimed particle size, and that also has substantially the same γ-IFN activity compared with the liquid prior to aerosolization with substantially the same molecular size distribution after aerosolization?

FINDINGS OF FACT

FF1 According to the Specification, "[m]ost current γ-IFN therapies involve administering the protein by injection." (Spec. 1.)

> By contrast, administering γ-IFN by inhalation, which requires aerosolizing the protein from a solution of γ-IFN, presents several challenges. In particular, it has not been known heretofore whether and how γ-IFN could be aerosolized without loss of activity and/or protein aggregation, particularly where the aerosol is formed under shear conditions necessary to produce a desired aerosol particle size range. This uncertainty is due in part to the fact that gamma [interferon] is active in a non-covalent dimeric form, but not in monomeric form. In addition, protein aggregation would be expected to reduce activity. Nor has it been known or [sic] how γ-IFN could be formulated so that its activity and molecular-size characteristics

> are maintained over an extended storage condition, yet still allow the desired protein properties and particle-size feature in an aerosol.

(*Id.* at 2.)

FF2 The invention is drawn to, in one respect, an aerosol composition for delivery to a patient's respiratory tract (*id.* at 3). The aerosol is formed by placing an aqueous γ-IFN solution having a known, selected γ-IFN activity, and also containing a stabilizing agent and a dispersing agent, against a plate having defined-size openings (*id.* at 3-4). "The droplets are characterized by a γ-IFN biological activity and molecular size distribution substantially the same as that of the aqueous γ-IFN solution." (*Id.* at 4.)

FF3 The Examiner rejects claims 16-23 and 25-28 over the combination of Huland, Debs, and Ruskewicz, as further evidenced by Nayar or Hora (Ans. 3). The Examiner also rejects claims 16-23 and 25-28 over the combination of Huland, Jaffe, Debs, and Ruskewicz, as further evidenced by Nayar or Hora (Ans. 6).

FF4 Huland is cited for teaching "various aerosol compositions containing cytokines for reducing lung afflictions." (Ans. 3.) According to the Examiner, the cytokines are combined with mannitol (reads on the stabilizing agent) and polysorbate, such as polysorbate 80 (reads on the dispersing agent) (*id.*). The Examiner notes that while Huland "describe[s] cytokine IL-2 extensively, they also describe interferon gamma." (*Id.* at 4.)

FF5 Specifically, Huland teaches that local administration of cytokines leads to fewer side effects than found with systemic administration (Huland, col. 1, l. 41 to col. 2. l. 46). Huland is thus drawn to a

> method for treating a patient having at least one affliction selected from infections, immunodeficiency syndromes, inflammatory diseases, autoimmune diseases, foreign body transplants, or requiring immuno regulation of tumor diseases. The method comprises causing such a patient to inhale an amount of a nebulized aerosol composition effective to reduce the affliction. The aerosol composition consists essentially of a solution of at least one cytokine, at least one serum protein, and a sufficient amount of a pharmaceutically acceptable aqueous carrier solution therefor to form a homogeneous solution. The carrier contains at least one component selected from the group consisting of a pharmaceutically acceptable salt, buffer and sugar.

(*Id.* at col. 4, ll. 18-30.) Moreover, Huland teaches that the cytokine used may be interferon gamma (γ-IFN) (*id.* at col. 4, ll. 45-55).

FF6 The Examiner acknowledges that Huland "does not expressly discuss the volume diameter of the droplets used in the delivery." (Ans. 4.)

FF7 Jaffe is cited for teaching "rIFN - γ formulated in an excipient composed of sodium succinate, mannitol, and polysorbate 20." (*Id.* at 7.) Jaffe is further cited for teaching that "the aerosol droplets were in the size range of 0.2-3μm allowing for deposition in the lower respiratory tract." (*Id.*)

FF8 Jaffe further teaches that alveolar macrophages were activated, and that the inhalation of rIFN-γ was not associated with local or systemic adverse side effects (Jaffe, abstract).

FF9 Debs is cited for teaching "the use of aerosolized IFN-gamma to stimulate alveolar macrophage and blood monocyte function." (Ans. 4.)

FF10 Ruskewicz is cited for its description of an aerosol extrusion mechanism, which teaches that when a pharmaceutical formulation is forced

through the flexible porous membrane, an aerosol is formed that has a particle size in the range of 1 to 12 microns, and more preferably in the range of 3.0 to 6.0 microns (*id.*). Ruskewicz is also cited for teaching "that a compound can be directed to a particular area of the lung which needs treatment by adjusting the aerosol particles size." (*Id.*)

FF11 Specifically, Ruskewicz teaches that the aerosol particle size may be changed by adjusting the size of the pores of the membrane (Ruskewicz, col. 28, ll. 41-42.) Moreover, according to Ruskewicz:

> One aspect of the invention involves manipulating the particle sizes in order to treat particular areas of the lung. For example, when it is desirable to treat the outer most peripheral areas of the lung the method of the present invention involves reducing the particle size to a particle size in the range of 0.5 to 3 microns. *When it is desirable to treat the more central areas of the lung larger particle sizes are used and the particle size is adjusted to a size in the range of 5 to 9 microns*. In some instances it is desirable to treat both areas simultaneously and to deliver aerosolized drug wherein the particle size is distributed over two different ranges. For example, the particle size could be distributed closely to a size of about 2 microns (within the range of 0.5 to 3 microns) for one group of particles and distributed close to a particle size of about 7 microns (within the range of 5 to 9 microns). The smaller particles would reach and treat, primarily, the peripheral areas of the lungs whereas the larger particles would reach and primarily treat the central areas of the lungs. In some instances, the particle size distribution is kept relatively broad over a range of 0.5 to 9 microns.

(*Id.* at col. 28, ll. 20-40 (emphasis added).)

FF12 Thus Ruskewicz specifically teaches the use of particles distributed close to a particle size of about 7 microns (within the range of 5 to 9

microns), and thus teaches particle size within the range of 5-10 microns as specified in the Markush group of claim 22.

FF13 Nayar and Hora are cited for teaching "serum free stabilized proteins" (Ans. 5).

FF14 The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a γ-IFN composition containing a stabilizer such as mannitol and a dispersing agent such as polysorbate because Huland teaches aerosol composition comprising a cytokine, mannitol, and polysorbate and because Debs, as well as Jaffe, teaches the delivery of aerosolized γ-IFN to the respiratory system, and that the γ-IFN is capable of stimulating HLA-DR antigen expression (Ans. 5, 8). The Examiner also concludes that Ruskewicz teaches the aerosol extrusion mechanism, and it would have been obvious to adjust the aerosol particle size to a desired size to direct the aerosol composition to a particular area of the lung (*id.*).

PRINCIPLES OF LAW

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*

Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 1739. Moreover, an "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982).

Moreover:

> *Where . . . the claimed and prior art products are identical or substantially identical,* or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product…. Whether the rejection is based on "inherency" under 35 U.S.C. § 102, on "prima facie obviousness" under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

In re Best, 562 F.2d 1252, 1255 (CCPA 1977) (emphasis added.)

ANALYSIS

The Examiner rejects claims 16-23 and 25-28 over the combination of Huland, Debs, and Ruskewicz, as further evidenced by Nayar or Hora (Ans. 3). The Examiner also rejects claims 16-23 and 25-28 over the combination of Huland, Jaffe, Debs, and Ruskewicz, as further evidenced by Nayar or Hora (Ans. 6). As the rejections are essentially the same, we will treat them together. Moreover, as Appellants do not argue the claims separately, we

focus our analysis on claim 22, and claims 16-21, 23 and 25-28 stand or fall with that claim. 37 C.F.R. § 41.37(c)(1)(vii). We conclude that the Examiner has set forth a prima facie case of obviousness (*See, e.g.*, FF14), and we thus turn to Appellants' arguments in rebuttal.

Appellants argue that none of Huland, Debs, Nayar, or Hora, nor Jaffe, teaches a γ-IFN composition having the claimed particle size (App. Br. 4, 8), and that while Ruskewicz discloses "'an aerosol preferably having a particle size in the range of about 1 to 12 microns, more preferably of about 3.0 to 6.0 microns,'" Ruskewicz "does not teach or suggest the claimed particle size range of: (i) less than 1 micron, (ii) 1-3 microns, (iii) 3-5 microns, (iv) 5-10 microns, or (v) greater than 10 microns." (*Id.* at 5 (quoting Ruskewicz, col. 17, ll. 58-60).)

Appellants' argument is not convincing, as Ruskewicz specifically teaches the use of particles distributed close to a particle size of about 7 microns (within the range of 5 to 9 microns), and thus teaches the size range of 5-10 microns as specified in the Markush group of claim 22 (FF12). Moreover, even in the absence of that teaching, we find that the claimed particles size ranges would have been obvious as it would have been well within the level of skill in the art to determine and produce an aerosol with any desired particle size as Ruskewicz teaches that the aerosol particle size may be changed by adjusting the size of the pores of the membrane (FF11). Particle size was recognized in the art as a result-effective variable (FF11).

Appellants argue further that "[n]one of the cited references . . . describe an aerosol droplet composition of γ-IFN with retention of substantially similar γ-IFN activity compared with the liquid prior to

aerosolization" (App. Br. 6), nor do any of the cited references teach "a composition of γ-IFN with substantially the same molecular size distribution after aerosolization" (*id.* at 7).

Again, we do not find Appellants' arguments convincing. The combination of references teaches a composition having all of the components of the aerosol composition of claim 22. That is, the combination teaches a γ-IFN aerosol composition comprising a dispersing agent and a stabilizing agent, such as a sugar, having the claimed defined-size droplet particles. The claimed properties of retention of substantially the same γ-IFN activity compared with the liquid prior to aerosolization and having substantially the same molecular size distribution after aerosolization would then be inherent properties of that composition which is otherwise suggested by the prior art, and thus the burden has been properly shifted to Appellants to demonstrate that the prior art products do not necessarily or inherently possess the characteristics of the claimed product.

CONCLUSIONS OF LAW

Thus, we conclude that the Examiner has established a prima facie case of obviousness, and that the combination teaches γ-IFN aerosol composition having the claimed particle size, and that also has substantially the same γ-IFN activity compared with the liquid prior to aerosolization with substantially the same molecular size distribution after aerosolization. The obviousness rejections are therefore affirmed.

TIME LIMITS

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

cdc

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